# **REVIEW**



# Current state and future

prospects of pharmacological interventions for autism

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# **Practice points**

- Treatment of core and associated symptoms of autism spectrum disorder (ASD) should be multimodal.
- Use of medication should be directed toward specific, clearly identified target symptoms.
- The only US FDA-approved medications in individuals with ASD are risperidone and aripiprazole. They are both approved for the treatment of irritability in youth with autism.
- Children with ASD appear to have more adverse effects to selective serotonin-reuptake inhibitors inhibitors compared with adults when being treated for repetitive behaviors.
- Children with ASD develop more adverse effects to stimulant medication for the treatment of hyperactivity compared with their peers.
- Use of atypical antipsychotics in individuals with ASD warrants careful examination and monitoring of cardiometabolic parameters.

SUMMARY Autism spectrum disorder (ASD) is a group of heterogeneous developmental disorders manifesting in early childhood. They are associated with a range of core and associated symptoms, including repetitive behaviors, hyperactivity and irritability. This review will describe the current evidence for psychopharmacological management of individuals with ASD. Additionally, some of the future treatment prospects will be discussed. Safety issues, adverse effects and limitations of the current literature will also be highlighted.

Autism spectrum disorder (ASD) are a group of Asperger's disorder and pervasive developmenheterogeneous developmental disorders manifesting in early childhood. ASD encompasses DSM-IV-TR diagnoses of autistic disorder,

tal disorder not otherwise specified (PDD-NOS) [1]. ASD is diagnosed through the presence of core deficits that include impairments in social



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interaction and communication along with interfering repetitive behaviors and restricted interests. In addition, individuals with ASD suffer from symptoms of hyperactivity, anxiety, sleep disturbances and irritability. The latter symptom grouping can be seen in the form of severe tantrums, aggression and self-injurious behavior. Currently, only risperidone [2] and aripiprazole [3] are US FDA approved for individuals with ASD. Specifically, they have the indication for the symptoms of irritability. As the core and associated symptoms of ASD have a substantial negative impact on individual and family functioning, other psychotropic medications have been prescribed off label. This practice has led to over half of children and adults with ASD being prescribed psychotropic medications [4,5]. The most common drug classes include antipsychotics, antidepressants and stimulants. In this review, we will report upon the current evidence for psychopharmacological interventions in individuals with ASD. We will also discuss potential future treatment directions.

# Target symptom identification & practical issues in psychopharmacological treatment

Intervention strategies for ASD are multidisciplinary and include medication, behavioral interventions, speech and language therapy, social skills training, physical therapy and occupational therapy.

Effective psychopharmacological treatments for the core symptoms of ASD remain largely elusive. It is therefore import to identify specific target symptoms when considering commencement of a medication. Target symptoms that are commonly encountered include irritability (including aggression), repetitive or stereotyped behaviors, and hyperactivity.

It appears that the use of atypical antipsychotics may be beneficial in reducing aggression and irritability in both children and adults with ASD. Low-dose initiation with gradual titration based on symptom improvement is a prudent approach given the propensity for adverse effects in individuals with ASD. Atypical antipsychotics have been associated with a plethora of cardiometabolic changes, and in this regard it is important to monitor weight changes and laboratory tests such as fasting glucose, lipid profile and glycosylated hemoglobin. In individuals who demonstrate only mild irritability or aggression, a trial of an  $\alpha$ 2-adrenergic agonist (e.g., clonidine) may be considered prior to an atypical antipsychotic.

Repetitive and stereotyped behaviors are another commonly identified group of target symptoms. Treatment of repetitive behaviors with selective serotonin-reuptake inhibitors (SSRIs) may be beneficial and well tolerated in adults with ASD. Younger individuals with ASD may demonstrate less benefit from SSRIs while having greater adverse effects. A trial of an SSRI may still be undertaken in younger individuals with repetitive behaviors, although initiation at a low dose with cautious dose titration may be prudent. Proactive monitoring for adverse effects, such as behavioral activation, would also be highly recommended.

### Review of current pharmacological treatments in autism by medication class Atypical antipsychotics

Atypical antipsychotics are commonly prescribed for the treatment of irritability in ASD. Studies have shown that 24-31% of individuals with ASD have taken an atypical antipsychotic. This has led to this class of medications accounting for the majority of prescriptions in the ASD population [4,5]. Specifically, irritability has been noted to decrease from baseline on the Aberrant Behavior Checklist - Community Irritability Subscale (ABC-I) rating scale [6]. Unfortunately, this class of medications is associated with multiple side effects that include tardive dyskinesia, akathisia, metabolic syndrome and extrapyramidal symptoms (EPS). Physicians need to closely monitor for all side effects of medications which should be based on clinical judgment but include regular blood work and administration of the Abnormal Involuntary Movement Scale (AIMS) [7].

Weight gain is a particularly worrisome side effect associated with atypical antipsychotics. While there is a considerable degree of individual variation, both clozapine and olanzapine are associated with the highest levels of weight gain [8]. Risperidone and quetiapine have moderate levels, while aripiprazole and ziprasidone have the lowest associated levels. Weight is an important clinical parameter to measure given that atypical antipsychotic-associated dyslipidemia and glucose dysregulation combined with obesity can heighten cardiometabolic risk.

#### Risperidone

In 2006, risperidone became the first medication to gain FDA approval for the treatment of irritability in children and adolescents with ASD aged 5-16 years. Risperidone remains the most studied atypical antipsychotic medication for irritability. Evidence for its efficacy stemmed from work undertaken by the Research Units on Pediatric Psychopharmacology (RUPP) Autism Network [9]. The first trial was an 8-week, double-blind, placebo-controlled trial involving 101 children (male: 82; female: 19) aged 5-17 years [9]. Children were deemed to be responders if they had a 25% improvement in the ABC-I subscale and a rating of 'much improved' or 'very much improved' on the Clinical Global Impressions - Improvement (CGI-I) scale. The majority of children given risperidone were responders (69%), with a 56.9% decrease in their ABC-I score. There was also a significant improvement in both ABC stereotypy and hyperactivity subscales when risperidone and placebo groups were compared (p < 0.001). Final mean risperidone dosages were relatively low at study end point (mean: 1.8 mg/day). Further evidence for efficacy of risperidone for irritability stemmed from another similarly designed randomized, placebo-controlled trial involving 79 children [10]. Children given risperidone (mean dosage: 1.2 mg/day) demonstrated significant reductions in their ABC-I scores compared with placebo. Additionally, risperidone-treated participants had significantly decreased hyperactivity, conduct problems, anxiety and stereotypic behavior. Risperidone was well tolerated with only one participant withdrawing due to adverse effects. While somnolence was initially reported in 72.5% (n = 29) of risperidonetreated participants, it resolved in 86.2% of these individuals (n = 25).

The above-mentioned RUPP Autism Network study also included a separately reported 16-week open-label extension phase, in which previous risperidone responders were continued on the drug and closely monitored [11]. A total of 63 children participated in this phase with maintenance of response in over 80% of the participants. The CGI-I and ABC-I scores were maintained as the measurement outcome scales. Of note, a gradual substitution of risperidone with placebo resulted in a significant return of aggression, temper tantrums and self-injurious behavior. Analysis from the initial and extension parts of this study highlighted significant improvements in affect, sensory and motor ratings when risperidone was compared with

placebo. The study did not show improvements in social interaction or communication [11].

There has been less research focusing on the use of risperidone in adults with ASD compared with children and adolescents. A double-blind, placebo-controlled study involving 31 adults with ASD noted 57% as being responders to risperidone (mean dose: 2.9 mg/day). Treatment response was defined by a CGI-I score of 'much improved' or 'very much improved' [12]. Risperidone demonstrated superiority compared with placebo in reducing repetitive behavior, aggression, anxiety, depression and irritability. As was the case with children and adolescents, risperidone did not significantly improve social interaction or communication compared with placebo.

In regard to risperidone's side-effect profile, it appears to be generally well tolerated in both children and adults. Significant weight gain and increased appetite have been noted in children [9]. Sedation is also commonly encountered in both children and adults but generally appears to be self-limiting [9,12]. Dosages of risperidone used in the studies did not lead to any significantly greater EPS or evidence of tardive dyskinesia compared with placebo [9,13].

#### Aripiprazole

Aripiprazole is another atypical antipsychotic that has FDA approval for the treatment of irritability associated with ASD in children aged 6-17 years. Two large 8-week, double-blind, placebo-controlled studies (combined n = 316) demonstrated significant improvement in the ABC-I scores when aripiprazole was compared with placebo [3,14]. The first of these studies included 218 participants who were randomized in a 1:1:1:1 ratio to aripiprazole (5, 10 and 15 mg) and placebo [3]. Significant improvements were seen in CGI-I scores with all dosages of aripiprazole compared with placebo. Aripiprazole was generally well tolerated with only two serious adverse events: one case of presyncope and one case of increased aggression [3]. The second study included 98 participants (mean age: 9.3 years), of which 47% were randomized to aripiprazole (mean end dose: 8.9 mg/day). Significant improvements in irritability per ABC-I scores and global improvement (CGI-I) were recorded over the course of 8 weeks for aripiprazole compared with placebo. While no serious adverse effects were reported, weight gain and the development

of EPS were greater for aripiprazole compared with placebo [3].

In addition, there have been several open-label studies that support the short-term effectiveness and tolerability of aripiprazole in children with ASD [15,16]. A recently published 52-week open-label study investigated the long-term efficacy of aripiprazole in children with ASD [17]. Aripiprazole was administered using a flexibledosing schedule (mean end dose at week 52: 10.6 mg/day). Children who were responding to aripiprazole on entry into the study maintained their improvements in global ratings and irritability throughout its duration while children who were started on the drug demonstrated reductions in both irritability and global impressions. At week 52, children who were newly trialed on aripiprazole also demonstrated improvements in social withdrawal, stereotypic behavior, hyperactivity and inappropriate speech [17]. A further analysis of the findings of this study reported on the safety and tolerability of aripiprazole [18]. Adverse effects were encountered by 86.7% of participants. Most commonly, weight gain, increased appetite, gastrointestinal upset, insomnia, nasopharyngitis and upper respiratory tract infections were found in participants. Discontinuation of aripiprazole occurred in 10.6% of participants due to weight gain and aggression. Some 14.5% of the participants experienced EPS, most commonly tremor, psychomotor hyperactivity and akathisia.

Unfortunately, there is a lack of research on the use of aripiprazole in adults with ASD. One case series of five adults with ASD, of normal intelligence, with heterogeneous symptoms and comorbid diagnoses noted that the majority (n = 4) experienced improvement in a range of 'challenging behaviors' with aripiprazole [19].

#### Paliperidone

Paliperidone, also known as 9-hydoxyrisperidone, is the major active metabolite of risperidone but does not have FDA approval for any symptoms of ASD. A case series of two individuals with ASD, aged 16 and 20 years, described a reduction in irritability with the use of paliperidone [20]. More recently, an 8-week, open-label study involving adolescents and young adults with ASD (n = 25) investigated the role of paliperidone in reducing irritability [21]. This study demonstrated a response in 84% of participants, as determined by scores on the CGI-I and ABC-I. Paliperidone was generally well tolerated. Notable adverse effects included mild-to-moderate EPS (n = 4) and weight gain (mean weight gain: 2.2 kg).

#### Quetiapine

Quetiapine is an atypical antipsychotic medication that does not have FDA approval for any ASD symptoms but has been investigated in retrospective and open-label studies in ASD. A 12-week, open-label trial of quetiapine was conducted in nine males with ASD, aged 10-17 years with a mean dose of 291.7 mg/day and a dosage range of 100-450 mg/day [22]. Only two of the nine participants were responders based on the CGI-I but adverse effects were common, including sedation and weight gain in most participants. Two individuals dropped out of the trial due to increased aggression/agitation (n = 1) and increased drowsiness (n = 1), respectively. Additionally, elevated agitation was noted in almost half of the population (four of nine) with two participants demonstrating more aggressive behaviors [22].

Another small open-label study investigated the use of low-dose quetiapine (mean dose: 123 mg/day) in adolescents with ASD (n = 11) [23]. Significant improvements in sleep and aggression were noted, as measured by the Overt Aggression Scale (OAS) and Child Sleep Habits Questionnaire (CSHQ). In this trial, quetiapine was relatively well tolerated with only mild adverse effects of nausea (n = 1) and a decrease in appetite (n = 2). No significant change in bodyweight was noted over the 8-week study period.

Retrospective chart reviews on the use of quetiapine in ASD have also been conducted that have provided some positive evidence for the effectiveness of quetiapine. A large retrospective review identified 20 patients with ASD treated with quetiapine (mean age: 12 years; range: 5-28 years). A total of 40% of patients had responded to quetiapine at a mean dosage of 248.7 mg/day over an average duration of 59.8 weeks. Unfortunately, quetiapine-related adverse effects were found in 50% of patients, which resulted in drug discontinuation in 15% of the sample. A second retrospective review of ten children and adolescents (mean age: 12 years) noted six (60%) were responders based on the Conners Parent Scale (CPS). Improvement was found in ASD children's conduct, inattention and hyperactivity subscales of the CPS [24]. Compared with other studies, participants utilized higher dosages of quetiapine (mean dose: 477 mg/day)

but over a shorter mean duration of 22 weeks. The adverse effects encountered were described as generally mild. Sedation was seen in three patients (30%), and three patients (30%) experienced marked weight gain in excess of 10 lb.

#### Olanzapine

Olanzapine is a non-FDA-approved atypical antipsychotic medication for ASD that has some evidence for use in individuals with ASD. There has been one placebo-controlled study of olanzapine exploring global functioning and impulsivity/aggression in 11 ASD children and adolescents (mean age: 9 years; range: 6-14 years) [25]. Response, as defined by the CGI-I scale, was seen in 50% (n = 3) of the olanzapine group and in 20% of the placebo group (n = 1). The olanzapine-treatment cohort (mean dose: 10 mg/day; range: 7.5-12.5 mg/day) showed more weight gain than placebo (7.5 vs 1.5 lb).

A recent open-label study of olanzapine in 40 male children (mean age: 12.2 years) noted significant improvements in irritability, lethargy, stereotyped behavior, hyperactivity and inappropriate speech [26]. No significant increases in weight or metabolic abnormalities were seen in the study. Another 12-week open-label study investigated the efficacy and tolerability of olanzapine in treating core and associated symptoms of ASD [27]. Eight patients (mean age: 20.9 years; range 5-42 years) were recruited. A total of 75% (n = 6) of the olanzapine (mean dose: 7.8 mg/day) group demonstrated improvement in their CGI-I. They were noted to have significant improvements across many domains including hyperactivity, social relatedness, aggression, irritability and anxiety. There was no change noted in repetitive behaviors. Side effects included weight gain and increased appetite in the majority of participants (75%), with a mean weight gain of 18.44 lb (13% increase in bodyweight) at completion of the 12-week study. Sedation was a problem for three patients but no participants suffered from EPS [27].

#### Ziprasidone

Ziprasidone is another atypical antipsychotic medication that does not have FDA approval for ASD, but has demonstrated some effectiveness in open-label studies and a retrospective chart review. The retrospective chart review was conducted on the effect of ziprasidone in ten adults with ASD [28]. Patients included individuals who had been switched from another atypical antipsychotic due to weight gain. They had to be treated with ziprasidone for at least 6 months to be included in the study. Results showed seven of the ten patients had no change or an improvement in maladaptive behavior once they had been switched to ziprasidone. The majority of patients (n = 8) experienced weight loss averaging 13.1 lb. Metabolic monitoring was undertaken in five of the ten patients. Three patients had decreased triglyceride levels (60%) and four had decreased total cholesterol levels (80%).

A 6-week open-label study of ziprasidone in adolescents with ASD (n = 12; mean age: 14.5) reported outcomes based on CGI-I, ABC and the Children's Psychiatric Rating Scale [29]. The majority of participants (n = 9 [75%]) who received ziprasidone (mean dose: 98.3 mg/day; range: 20–160 mg/day) were responsive to treatment based on CGI-I score improvement. Ziprasidone appeared weight neutral or even led to a decrease in weight. Although not clinically significant, participants were noted to have an increase in their QTc interval on electrocardiogram of 14.7 ms. Two participants developed acute dystonic reactions during the study.

A case series of ziprasidone in 12 patients with ASD (mean age: 11.6 years; range: 8–20 years) was completed [30]. Patients received ziprasidone (mean dose: 59 mg/day; range: 20–120 mg/day) for at least 6 weeks (mean duration: 14 weeks; range: 6–30 weeks). A total of 50% (n = 6) of patients were noted to be responders according to the CGI-I changes. Ziprasidone seemed to be well tolerated as no cardiovascular adverse effects were noted. Transient sedation was encountered in 75% of patients (n = 8). A mean weight loss of 5.83 lb was found in patients on ziprasidone that was atributed to discontinuation of other atypical antipsychotic medications that had resulted in weight gain.

#### Clozapine

Clozapine was the first atypical antipsychotic medication licensed in the USA. There have only been limited reports of its use in individuals with ASD and thereby there has been no FDA approval for any indication in this population. One retrospective chart review reported that six patients with ASD demonstrated reduced aggression with clozapine treatment. Constipation and weight gain were the most prominent adverse effects noted [31].

The role of clozapine in ASD appears to be limited because of its possible significant

adverse effects. For example, clozapine can markedly lower the seizure threshold, an important consideration in ASD, as at least one in five affected individuals may also have epilepsy [32]. Additionally, clozapine may induce agranulocytosis, necessitating mandatory hematological monitoring. This makes clozapine less appealing in ASD since many individuals with ASD have profound distress during medical interventions such as venipuncture [33].

#### Typical antipsychotics

Typical antipsychotics may be used in individuals with ASD to reduce irritability. They are less commonly used than the second-generation antipsychotics due to concerns regarding EPS and the greater risk of the development of tardive dyskinesia. They remain a consideration in individuals who do not respond to atypical antipsychotics, require intravenous/intramuscular formulations or have considerable cardiometabolic morbidity.

#### Haloperidol

Haloperidol was one of the first medications used in treating children with ASD. There is some evidence suggesting it may lead to symptomatic improvement in ASD [34]. A doubleblind, placebo-controlled, crossover study investigated the use of haloperidol, clomipramine and placebo in a wide age range of participants with ASD (mean: 16.3 years; range: 10-36 years) [35]. Haloperidol administration resulted in improvements in irritability and hyperactivity as measured by the ABC-I. In addition, haloperidol had superior improvements in the Childhood Autism Rating Scale (CARS) when compared with baseline. Of note, over 30% (n = 10) of individuals did not complete the haloperidol portion of this trial. Discontinuation of haloperidol was attributed to behavioral disturbances, fatigue, depression and one case of dystonia. Haloperidol has been linked to the development of tardive dyskinesia in children with ASD, with greater cumulative dose and longer duration of treatment being risk factors [36].

Despite proven efficacy in treating a range of ASD symptoms, the use of haloperidol is limited by the associated EPS side effects, acute dystonic reactions, dyskinesias and risk of tardive dyskinesia. Haloperidol should be typically limited to more treatment-resistant cases.

# Cholinesterase inhibitors (donepezil, rivastigmine & galantamine)

ASD patients have demonstrated marked impairments in executive function [37]. This fact, combined with evidence suggesting cholinergic abnormalities in ASD [38], has led to trials of cholinesterase inhibitors. Evidence for their use in ASD remains limited although some findings from open-label studies have been encouraging.

One 12-week open-label study of donepezil in 25 children (mean age: 6.6 years) with ASD noted an improvement of expressive speech [39]. No significant change in global measures of autism was observed, as noted by the CARS. Despite the low doses of donepzil (2.5-5 mg/day), adverse effects included aggression, irritability, lethargy and disturbed sleep. A recent 10-week, double-blind, placebo-controlled trial of donepezil was conducted to assess cognitive functioning in children and adolescents with ASD [40]. Participants were older than in the prior open-label study, with a mean age of 11.5 years (range: 8.6-16.7 years). Unfortunately, executive functioning did not significantly differ when donepezil was compared with placebo. Donepezil was well tolerated, with only an increase in diarrhea, headache and fatigue being reported.

Limited studies have been undertaken assessing the other anticholinesterase inhibitors such as rivastigmine and galantamine. A 12-week, open-label trial of rivastigmine involving 32 children (mean age: 6.9 years) noted significant improvements in both expressive speech and behavior. These results were obtained from both parental report and standardized rating scales [41]. Galantamine was studied in a 12-week, open-label trial involving 13 children (mean age: 8.8 years) [42]. Irritability and social withdrawal were improved as assessed by the ABC. Furthermore, emotional liability and inattention were less frequently reported per the Conners Parent Rating scale–Revised and 61.5% (n = 8) showed improvement on the CGI-I. Galantamine appeared to be well tolerated with only one patient developing headaches.

#### Serotonin-reuptake inhibitors

ASD has been linked to a plethora of abnormalities in serotonergic neurotransmission, including hyperserotonemia, aberrant serotonin synthesis and alterations in serotonin receptor binding in the brain [43–45]. Adults with ASD have been described as having increased autistic behaviors associated with short-term dietary depletion of tryptophan, a precursor of serotonin [46]. Repetitive behaviors, a core symptom of ASD, have been suggested as being similar to the compulsions seen in obsessive compulsive disorder. Serotonin-reuptake inhibitors are FDA approved for the treatment of obsessive–compulsive disorder, so this has led to questions of their efficacy for repetitive behaviors observed in ASD. Thus, the evidence for underlying serotonergic disturbance in ASD and commonalities with obsessive–compulsive disorder has led to investigation of medications that affect serotonergic neurotranmission.

The use of SSRIs in children and adolescents should be accompanied by regular assessment of suicide risk. The importance of this is highlighted by a 2004 FDA black box warning describing the possibility of increased suicidality in children and adolescents on SSRIs.

#### Clomipramine

Clomipramine is a nonselective serotoninreuptake inhibitor that also inhibits norepinephrine and dopamine reuptake [47]. Two doubleblind, placebo-controlled, crossover studies have evaluated the use of clomipramine in children with ASD. A small (n = 24) 10-week crossover study compared clomipramine with placebo, and a relatively selective norepinephrine-reuptake inhibitor, desipramine [48]. Clomipramine, at a mean dose of 152 mg/day, was superior to both placebo and desipramine in improving standardized ratings of autism, anger and repetitive/compulsive behaviors. Both clomipramine and desipramine were superior to placebo in improving hyperactivity. Clomipramine side effects included insomnia, constipation and sedation but no statistically significant difference was found in adverse effects between clomipramine, desipramine and placebo. However, clomipramine dosage was reduced in two participants. This change in dose was due to an episode of tachycardia (160-170 beats/min) and QTc prolongation (450 ms). One subject had to withdraw from the study after experiencing a seizure while taking 75 mg/day of clomipramine.

A second small crossover study (n = 36) of clomipramine (mean dose: 128.4 mg/day; range: 100–150 mg/day) versus haloperidol in individuals with ASD (mean age: 16.3 years; range: 10–36 years) was conducted [35]. The clomipramine group had a significantly higher drop out rate compared with the haloperidol cohort (37.5 vs 69.7%). Clompiramine's adverse effects caused more than half of the discontinuations. The remaining discontinuations were due to behavioral disturbances [35]. Other adverse effects encountered with clomipramine included tremors, tachycardia, fatigue, nausea and decreased appetite.

A 12-week, open-label trial of clomipramine (mean: 139 mg/day) in 35 adults with ASD was conducted [49]. Results demonstrated 51% of participants (n = 18) responded to clomipramine based on their CGI-I rating. They showed significant improvements in repetitive behavior, aggression and social interaction [49]. Unfortunately, clinically significant adverse effects were encountered in 37% (n = 13) of patients. Three participants had seizures of which two had a previous history of seizures, and were taking anticonvulsants. No cardiovascular or EPS-related adverse effects were recorded.

### Citalopram

Citalopram, an SSRI, has been investigated for the treatment of repetitive behavior in children and adolescents with ASD. Evidence has revealed mixed findings regarding efficacy. Two retrospective chart reviews (combined n = 32) have noted that citalopram at dosages ranging between 5 and 40 mg led to significant improvements in CGI-I scores in 59–73% of participants [50,51].

The first study reviewed the impact of citalopram on aggression, anxiety, stereotypies and preoccupations in 17 children and adolescents with ASD (mean age: 9.4 years; range: 4-15 years). Patients had received citalopram (mean dose: 19.7 mg/day; range: 5-40 mg/day) for a minimum of 2 months (mean duration: 7.4 months; range: 1-15 months). Improvement in target behaviors was reported for 59% of patients (n = 10). Social interaction and communication did not change from baseline. Citalopram appeared well tolerated even though four patients developed adverse effects that limited treatment. These effects included two cases of increased agitation, one case of insomnia and one case of possible tics. The second study reported on 15 children and adolescents with ASD (mean age: 11.1 years; range: 6–16 years) who were treated with citalopram (mean dose: 16.9 mg/day; range: 5-40 mg/day). Citalopram treatment (mean duration: 219 days) led to improvement in of anxiety and mood symptoms. Mild adverse effects were noted in 33% of the children.

A larger (n = 149), multisite randomized controlled trial investigated the use of citalopram on repetitive behaviors in ASD [52]. This 12-week trial included children and adolescents (mean age: 9.4 years old) who had ASD in addition to moderate problems with repetitive behavior as scored on the Children's Yale-Brown Obsessive Compulsive Scales modified for pervasive developmental disorders (CYBOCS-PDD). No significant differences were noted between citalopram (mean dose: 16.5 mg/day) and placebo in relation to clinical improvement (CGI-I) or repetitive behaviors. The citalopram cohort did experience higher levels of adverse effects including hyperactivity, stereotypy, diarrhea, insomnia and impulsiveness.

#### Escitalopram

Escitalopram is an SSRI and a (S)-enantiomer of citalopram. One open-label study has explored its use in 28 children and adolescents (mean age: 10.4 years) with ASD [53]. Response was seen in 61% of participants at a mean dose of 11.1 mg/day (range: 0–20 mg) per the ABC-I. Significant improvements were shown for hyperactivity, lethargy, inappropriate speech and stereotypy. Dose-related adverse effects requiring dose reduction were noted in 64% (n = 18) of participants. Adverse effects encountered were primarily irritability and hyperactivity.

#### Fluoxetine

Fluoxetine is an SSRI that has been studied in the treatment of repetitive behaviors in ASD. Hollander *et al.* completed a 20-week placebocontrolled study involving 45 children and adolescents with ASD (mean age: 8.2 years; range: 5–16 years) who were given liquid fluoxetine (mean dose: 9.9 mg) [54]. Fluoxetine was superior to placebo in improving repetitive behaviors and on an assessment of effectiveness. Fluoxetine did not result in any significantly different adverse effects compared with placebo.

SOFIA is a large (n = 158) placebo-controlled trial of fluoxetine in the treatment of repetitive behaviors in ASD [101]. Children and adolescents (age range: 5–17 years) underwent 14 weeks of treatment with either placebo or fluoxetine. Preliminary findings have shown that fluoxetine was not effective in reducing repetitive behaviors compared with placebo. Further analyses of the study data are pending.

A double-blind placebo-controlled trial of fluoxetine in adults (n = 37; mean age:

34.3 years; range: 18–60 years) has also been reported [55]. Fluoxetine was better than placebo in improving repetitive behaviors as 50% of subjects given the drug were considered responders compared with only 8% given placebo. Despite relatively high dosages of fluoxetine (mean end point dose: 64.8 mg/day), there were only mild and moderate adverse effects. Most notably these included vivid dreams, insomnia, dry mouth and headaches.

#### Sertraline

Sertraline has been studied in a 12-week, openlabel study of adults with ASD (n = 42; mean age: 26 years; range: 18–39 years) [56]. Sertraline at a mean dosage of 122 mg/day was associated with a reduction in both aggression and repetitive behavior in 57% of participants [57]. An open-label study of sertraline in nine children (age range: 6–12 years) with ASD described improvements in irritability and anxiety at doses ranging from 25 to 50 mg/day over 2–8 weeks. Adverse effects were minor with one child developing abdominal pain and two other children exhibiting worsening behavior when sertraline doses were raised to 75 mg/day.

#### Fluvoxamine

Fluvoxamine is an SSRI that has had mixed results when used in ASD. Adults appear to tolerate it better and have a greater response when compared with children with ASD. A 12-week, double-blind, placebo-controlled study of adults with ASD reported 53% of the fluvoxaminetreated group as responders compared with zero in the placebo group [57]. Fluvoxamine was superior in reducing both repetitive and maladaptive behavior alongside aggression. Fluvoxamine at a mean dosage of 276.7 mg/day was well tolerated with only mild sedation and nausea noted.

The use of fluvoxamine in children has produced conflicting results. Positive evidence for the clinical effectiveness of fluvoxamine was derived from a 12-week, double-blind, placebo-controlled, randomized crossover study of 18 children with ASD [58]. Fluvoxamine treatment resulted in considerable improvement in 28% of cases (n = 5) and at least slight improvement in 56% of cases (n = 10), as rated by the CGI-I. Adverse effects such as hyperactivity and nausea were noted in 17 and 22% of participants, respectively. However, several studies in youth have not demonstrated beneficial outcomes with fluvoxamine. A 12-week,

future science group

double-blind, placebo-controlled study of children and adolescents with ASD (n = 34; mean age: 9.5 years; range: 5–18 years) demonstrated minimal response to fluvoxamine at a mean dose of 107 mg/day [59]. Only one of the 18 participants who was randomized to fluvoxamine demonstrated significant clinical improvement. Of note, 14 participants (78%) encountered adverse effects including insomnia (50%), hyperactivity (28%), agitation (28%), aggression (28%), change in appetite (22%) and anxiety (17%).

A 10-week, open-label study of 18 children and adolescents with ASD (mean age: 11.3 years) also noted no significant response to low-dose fluvoxamine (dosage range: 1–3 mg/kg/day) and three participants encountered behavioral activation necessitating fluvoxamine discontinuation [60].

#### Paroxetine

The SSRI paroxetine has undergone limited investigation for ASD. Several case reports have noted improvements in irritability in children and adolescents with ASD [61,62]. One study investigating the use of paroxetine in institutionalized adults with intellectual disability and ASD noted some short-term improvements in aggression [63].

#### Mirtazapine

Mirtazapine is a noradrenergic and specific serotonergic antidepressant and an  $\alpha$ 2-receptor antagonist. Several studies, including two openlabel studies, have investigated its use in ASD [64,65]. One naturalistic study assessed the efficacy and tolerability of mirtazapine over a mean duration of 150 days in 26 children and adolescents with ASD (mean age: 10.1 years; range: 3.8-25 years). The study found 35% of participants had improvement in symptoms such as irritability, hyperactivity, insomnia, depression and anxiety [65]. Mirtazapine did not demonstrate any improvements in the core ASD deficits of social interaction or communication. Adverse effects encountered included increased appetite, transient sedation and irritability [65].

Mirtazapine may be helpful in curbing excessive masturbation and other inappropriate sexual behaviors in children and adolescents with ASD [64]. An 8-week, open-label study of ten children and adolescents with ASD and excessive masturbation showed mirtazapine (mean dose: 21.6 mg/day) produced a 'much improved' or better clinical response in 80% of participants. Mirtazapine was well tolerated, although adverse effects of increased appetite, increased weight and sedation were documented.

#### Venlafaxine

Venlafaxine is a serotonin- and norephinephrinereuptake inhibitor that has some evidence, limited to case reports, for effectiveness in adults, children and adolescents with ASD [66,67].

A retrospective review of venlafaxine in ten individuals with ASD was conducted (mean age: 10.5 years; range: 3-21 years) [68]. Venlafaxine at relatively low doses (mean: 24.4 mg/day; range: 6.25-50 mg/day) was associated with clinical response (as defined by the CGI-I) in 60% of cases (n = 6). Participants demonstrated improvements in repetitive behaviors, socialization and language use. Symptoms of inattention and hyperactivity also improved.

#### Mood stabilizers Divalproex sodium

Divalproex sodium is both an anticonvulsant and a mood stabilizer. The anticonvulsant effect of divalproex sodium may be an important

clinical consideration in individuals with ASD who have comorbid epilepsy. Several open-label and placebo-controlled studies on divalproex sodium/valproic acid have reported mixed results on irritability associated with ASD.

A recent 12 week placebo-controlled trial with 55 children (mean age: 9.5 years) noted a significantly higher response (62.5%) based on improvements on the CGI-I in patients receiving divalproex sodium compared with placebo [69]. In addition, there was a significant improvement in ABC-I with the use of divalproex sodium. Interestingly, subjects who had valproate levels between 87 and 110 µg/ml had 100% response rates compared with 60% for valproate levels <87 µg/ml and 33% for levels >110 µg/ml. These findings supported an earlier retrospective study that noted a 71% response in 14 individuals with ASD when using a mean dose of 768 mg/day of divalproex sodium [70]. Symptomatic improvements were noted in associated symptoms (aggression, affective lability and impulsivity) and core symptoms of ASD.

In another double-blind, placebo-controlled study with 30 participants (range: 6–20 years) studied over 8 weeks, no significant difference was found between divalproex and placebo on the ABC-I (p = 0.65), CGI-I (p = 0.16) or the OAS (p = 0.96) [71]. Concerns were raised by the authors that the large placebo effect and small

sample size may be accountable for the lack of significant findings. Divalproex was generally well tolerated, although significantly increased appetite was encountered and two patients demonstrated elevated serum ammonia levels.

The use of divalproex sodium should be accompanied by monitoring of valproic acid levels. Additionally, liver function tests and complete blood counts should also be performed, given the risk of hepatotoxicity and thrombocytopenia, respectively. Clinicians should be aware of the symptoms of divalproex toxicity, including gastrointestinal upset, ataxia, tremor, confusion and sedation.

#### Lithium

Lithium, a simple metallic ion, was one of the first mood stabilizers used in clinical practice. The study of lithium in ASD has been limited to case reports [72,73]. Addition of lithium to fluvoxamine in an adult with ASD resulted in reduced aggression and irritability [74]. Clinical use of lithium requires monitoring of lithium serum levels as a result of its narrow therapeutic window. Lithium also requires both thyroid and renal function monitoring as a result of potential adverse effects on these organs. Lithium has also proven to be beneficial in reducing 'manic-like symptoms' in individuals with ASD who have a family history of bipolar disorder [73].

#### Lamotrigine

Lamotrigine is a mood stabilizer and an anticonvulsant with some limited reports of efficacy in ASD. One 12-week, double-blind, placebo-controlled study of 28 children (mean age: 5.8 years; range: 3-11 years) assessed the impact of lamotrigine on several core and associated symptoms of ASD [74]. No significant differences were found between lamotrigine and placebo in language and communication, social interaction, stereotypies, irritability and hyperactivity. The authors noted a marked improvement in the rating scales outcomes associated with placebo, which at times surpassed improvement noted with lamotrigine [74]. Another study that included children and adolescents with intractable epilepsy showed that in 13 participants who had comorbid ASD, eight had improvements in their core symptoms of autism with lamotrigine treatment [75]. The improvements in autistic symptoms was noted to be independent of the anticonvulsant effect.

# Glutamatergic agents (D-cycloserine & memantine)

There is a dearth of psychopharmacological research demonstrating improvements in social functioning or communication in ASD. An area for growth may lie in agents that modulate the *N*-methyl-D-aspartate receptor, a glutamate receptor. D-cycloserine is a partial N-methyl-D-aspartate agonist that has been found to be efficacious in the treatment of post-traumatic stress disorder and other anxiety disorders [76-78]. The effects of D-cycloserine on the social symptoms of ASD have been reported in one human study. An 8-week, single-blind study of individuals with ASD (n = 12; mean age: 10 years; range: 5.1-27.6 years) explored the effect of three different doses of D-cycloserine on social impairment [79]. D-cycloserine was associated with reduced social withdrawal and increased social responsiveness, with a clinical response evident in 40% of participants. D-cycloserine adverse effects were demonstrated in two participants, one who developed a transient motor tic and another who had an increase in echoalia.

A couple of studies have also reported on the use of memantine, a N-methyl-D-aspartate receptor antagonist, on the social symptoms of ASD. One open-label retrospective review of memantine (mean dose: 10.1 mg/day; mean duration: 19.3 weeks) was conducted in 18 children and adolescents with ASD (mean age: 11.4 years; range: 6–19 years) [80]. A response rate of 61% was reported based on the CGI-I, with symptom improvement principally seen in social withdrawal and inattention. Unfortunately, adverse effects were seen in 39% of cases, with increased irritability, increased seizure frequency, emesis and sedation being recorded. Similar positive findings were reported in an open trial of 151 individuals with ASD (mean age: 9 years; range: 2-26 years) where memantine had resulted in significant improvements in social behavior, language function and stereotypic behaviors [81].

There are several ongoing studies that are investigating the use of memantine in children with ASD. One randomized controlled trial is comparing memantine to placebo in children aged 6–12 years with ASD, with a particular focus on memory and executive function [102]. Another open-label study is also underway studying the safety profile of memantine in approximately 192 children with ASD, aged 6-12 years of age [103]. Both of these studies are due for completion in the latter part of 2013.

### Stimulant medication

Inattention and hyperactivity are symptoms that are commonly associated with ASD [82,83]. Studies have suggested that between half and three quarters of children with ASD have comorbid symptoms that would be compatible with an ADHD diagnosis [84,85]. Several placebo-controlled, double-blind, crossover studies have demonstrated positive results with the use of methylphenidate in the reduction of hyperactivity, stereotypy and inappropriate speech in children with ASD [86,87]. In one 3-week, double-blind, placebo-controlled, crossover study involving 13 children with ASD (mean age: 7.4 years; range: 5.6-11.2 years) and prominent hyperactivity, methylphenidate at two dosages (0.3 and 0.6 mg/kg) was compared with placebo [87]. Methylphenidate resulted in a significant response, as defined by a 50% or greater reduction in the Teacher Conners Hyperactivity Index in eight of the 13 children (62%). Improvements in inappropriate speech and stereotypies were also noted. Adverse effects were encountered, including social withdrawal and irritability, especially at the higher 0.6-mg/kg dosage. Two patients required discontinuation at this higher dosage, while one patient experiencing adverse effects on 0.3 mg/kg was not entered into the 0.6 mg/kg part of the study.

An 8-week, double-blind, placebo-controlled, crossover study with a 4-week open-label extension was completed on 72 children with ASD and prominent hyperactivity. The participants (mean age: 7.5 years; range: 5–14 years) had also undergone a 1-week test dose phase. Methylphenidate resulted in significant improvements in hyperactivity, with 49% of participants being classified as responders. Adverse effects, in particular increases in irritability, led to methylphenidate discontinuation in 18% of the participants. From these results the authors suggested that the response to methylphenidate in children with ASD was less than that seen with their non-ASD peers.

# α2-adrenergic agonists (clonidine guanfacine)

Extended-release formulations of the  $\alpha$ 2-adrenergic agonists clonidine and guanfacine are FDA approved for the treatment of ADHD in individuals aged 6–17 years of age. There have also been several studies exploring their use in individuals with ASD. Clonidine has been studied in two small controlled trials, resulting in improvements in hyperactivity, impulsivity and inattention [88,89]. Clonidine was, however, associated with sedation, fatigue, hypotension and irritability. It may be useful to conduct an ECG prior to using this group of medications, especially in individuals with cardiovascular comorbidities. Additionally this class of medications may potentially worsen or precipitate depressive symptoms.

# **Conclusion & future perspective**

The current corpus of evidence supporting the use of medications in individuals with ASD remains primarily focused on interventions in children and adolescents. Only a small number of trials have involved a randomized controlled design incorporating robust methodology. The evidence that is available suggests that children with ASD may be less responsive to serotonergic agents than adults, especially in the treatment of repetitive behaviors. As previously highlighted, patients with ASD may also be more susceptible to experiencing adverse effects. Overall, symptoms of irritability and hyperactivity/inattention both appear to respond well to antipsychotics and stimulants, respectively, although significant side effects are associated with each class of medication.

It is also important to recognize that many individuals with ASD are treated with polypharmacy. Very little research has focused on studying how combinations of medications may be effective for different target symptoms. This may very well be an area of future growth, especially as greater evidence of efficacy emerges from studies that are currently underway.

Interesting developments have also arisen from the study of oxytocin, an evolutionary ancient neuropeptide that has been associated with ASD [90,91]. A randomized, placebocontrolled, double-blind study investigated the use of intranasal oxytocin in 11 adults with ASD (mean age: 26 years; range: 17–39 years). Oxytocin administration resulted in increased visual scanning of facial images presented to participants, in particular to the region of the eyes. Oxytocin also appeared to improve the participant's response to social cues. Other similar studies have demonstrated improvements in emotional recognition in adolescents with ASD treated with intranasal oxytocin [92].

Future research will aim to identify subgroups of individuals with ASD potentially through a

combination of more specific clinical features, genetic testing and the identification of autism endophenotypes. These approaches may allow clinical studies to identify more homogenous groups of individuals with ASD. There are many other areas of active psychopharmacological research that are beyond the scope of this review but include specific molecular interventions in genetic conditions associated with ASD, such as fragile X syndrome [93], and also the potential for immune-modulating therapy in ASD [94].

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